CHEMISTRY LETTERS, pp. 1715-1718, 1982.

SYNTHESIS OF COMPOUNDS RELATED TO SCLEROSPORAL

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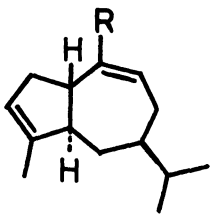
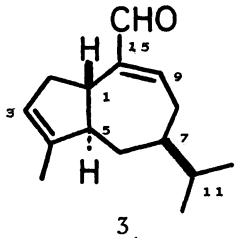
The proposed guaianoid structures for sclerosporal have turned out to be erroneous through synthesis of these structures, starting from (-)-carvone.

Sclerosporin, the major sporogenic substance of Sclerotinia flucticola, and its related metabolite, sclerosporal, were isolated by Marumo and co-workers[1] and were formulated as 1 and 2 respectively, by a trace-analytical technique. The proposed structures possessed the trans-guaiane skeleton, but the stereochemistry at C7, and the absolute configuration remained unsettled. For the purpose of confirming the structures of these metabolites, we have synthesized two optically active aldehydes, 3 and 4, possessing the proposed planar structure for 2.



1 R=COOH
2 R=CHO



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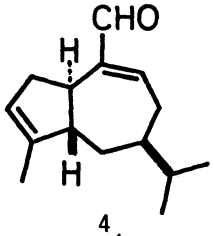

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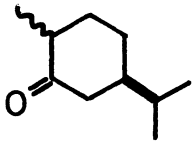

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Ketone 5,[2] prepared from (-)-carvone, was alkylated with 1,3-dibromo-2-pentene[3] (benzene, t-BuOK, reflux 3 h), and two stereoisomeric products were readily separated (silica gel, hexane-benzene 1:1, yield 6:55%, 7:22%). On treatment with $Hg(OAc)_2$(HCO_2H, rt, overnight),[4] a dione 8 and unexpectedly, a formate 10[5,6] were furnished from 6. Under similar conditions a dione 9 and a formate 11[5,6] were obtained from 7. The products were separated (silica gel, hexane-benzene 2:1) and the ratio of the dione and the formate was 9 to 2 (8 and 10 from 6, total 77% yield) and 3 to 4 (9 and 11 from 7, total 98% yield). The unprecedented formation of an allyl formate from a vinyl bromide may be explained by a mechanism shown in Scheme 1. However, it is clear that further study is necessary to confirm the suggested mechanism. Basic cyclization of each of the diones gave known enone 12[7,8] or 13.[7,8,9] Dehydrogenation of these 12 and 13 (DDQ, benzene, reflux 36 h, 65%) and subsequent photochemical rearrangement (45% AcOH-H_2O, 300 W high pressure mercury lump, 65%) gave 14, mp 107.6-107.8 °C, and 15, mp 142.7-142.9 °C, respectively.[10] Guaienones 14 and 15 were then reduced to

18[5] and 19,[5] mp 67-68 °C (Li-NH_3, 1.5 h, each about 65%). The trans ring fusion of 18 and 19 were elucidated by ORD curves (18: c 0.30($CHCl_3$) $[\alpha]_{319}$+1440(pk) $[\alpha]_{300}$=0 $[\alpha]_{272}$=-1760(tr); 19: c 0.38($CHCl_3$) $[\alpha]_{320}$=-2640(tr) $[\alpha]_{301}$=0 $[\alpha]_{278}$= +3672(pk)) according to Piers and Cheng's ORD study on the reduction products of 16 and 17.[11] The hydroxyketone 18 was then converted to its toxylhydrazone, which afforded 20[2] by basic degradation[12] (Na, ethyleneglycol, reflux 2 h, 68% from 18). Mesylation of 20 was secured by using 4-dimethylaminopyridine as base (10 eq of CH_3SO_2Cl and DMAP, CH_2Cl_2, -15 °C, then rt for 60 h), and treatment of the crude mesylate with basic alumina furnished a mixture 21[5] (82% from 20, $\Delta^{10(15)}$:Δ^{9}=1:2). The mixture was directly subjected to an allylic oxidation (0.1 eq SeO_2, excess t-BuOOH aq., 0 °C→rt 1 h). The desired allylic alcohol 22[5] and another alcohol presumed to be 23[5] were given (total 46%, 22:23=2:1). Further oxidation of 22 (MnO_2, benzene, rt, overnight) afforded an optically active aldehyde 3.

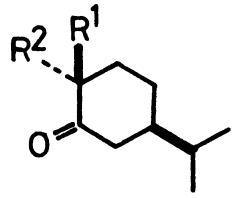
The isomeric aldehyde 4 was prepared from 19 in a similar sequence and similar yield.

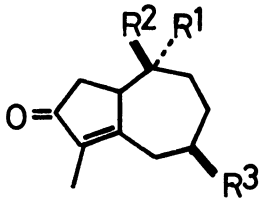
Comparison of the spectral data described below of the synthetic aldehydes 3 and 4 with those of natural aclerosporal demonstrates clearly that the proposed structure for sclerosporal must be revised. Furthermore, the structure 1 is also erroneous because it has been establihsed[1] that sclerosporin and sclerosporal are different only in the carbonyl functionality. Conformation of 3 and 4 as inferred by the coupling constants obtained from the nmr spectrum at 400 MHz, is shown in Fig 1.[13,14]

δ($CDCl_3$ 400 MHz) 3: 9.42(1H, s), 6.87(1H, ddd, J=8.8, 5.6, 2.4), 5.45(1H, bs), 1.64(3H, dd, J=3.2, 1.6), 0.92(3H, d, J=6.8), 0.90(3H, d, J=6.8). 4: 9.37(1H, s), 6.75(1H, ddd, J=8.4, 2.8, 2.8), 5.37(1H, bs), 1.67(3H, dd, J=2.4, 1.6), 0.91(3H, d, J=6.8), 0.90(3H, d, J=6.8). CD(hexane) 3: [θ]=-19000 (226nm), 4: [θ]=-27000 (223nm). λ_{max}^{hex} 3: 233nm (ε=13400), 4: 228nm (ε=14100). $[\alpha]_D$($CHCl_3$) 3: -83.3° (c 0.79, 4: -61.8° (c 0.80).

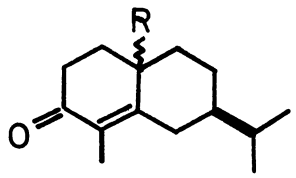
References

1) M. Katayama and S. Marumo, Tetrahedron Lett., 1979, 1773. S. Marumo and M. Katayama, Kagaku no Ryoiki, Special Issue No. 128, 42 (1980).
2) S. H. Schroeter and E. L. Eliel, J. Org. Chem., 30, 1 (1965) and refs. therein.
3) R. B. Ganmill and T. A. Bryson, Synthetic Commn; 1976, 209.
4) M. Julia and C. Blasioli, Bull. Soc. Chim. France, 1976, 1941. See also H. Yoshioka, K. Takasaki, M. Kobayashi, and T. Matsumoto, Tetrahedron Lett., 1979, 3489 and references cited therein.
5) Satisfactory infrared, ^1H NMR, and high resolution mass spectral data were obtained for this compound.
6) 10: m/z 266.1880 (Calcd for $C_{16}H_{26}O_3$ 266.1883), ν(neat) 1732, 1715 cm^{-1}. δ($CDCl_3$, 400 MHz) 8.02(1H, s), 5.79(1H, dt, J=14.5, 7), 5.48(1H, dd, J=14.5, 6.1), 5.45(1H, quint, J=6.1), 1.33 and 1.32(1:1)(3H, each d, J=6.1), 0.99 and 0.97(1:1)(3H, each s), 0.91 and 0.90(each 3H, d, J=6.1). Isomeric mixture.





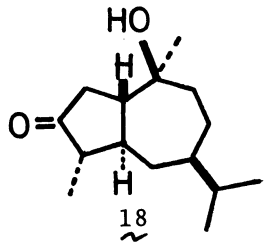
6 $R^1=CH_2CH=CHBrCH_2CH_3$, $R^2=CH_3$
7 $R^1=CH_3$, $R^2=CH_2CH=CHBrCH_2CH_3$
8 $R^1=CH_2CH_2COCH_2CH_3$, $R^2=CH_3$
9 $R^1=CH_3$, $R^2=CH_2CH_2COCH_2CH_3$
10 $R^1=CH_2CH=CHCH(OCHO)CH_3$, $R^2=CH_3$
11 $R^1=CH_3$, $R^2=CH_2CH=CHCH(OCHO)CH_3$



12 R=αCH$_3$
13 R=βCH$_3$

14 1βH, $R^1=CH_3$, $R^2=OH$, $R^3=CH(CH_3)_2$
15 1αH, $R^1=OH$, $R^2=CH_3$, $R^3=CH(CH_3)_2$
16 1βH, $R^1=CH_3$, $R^2=OH$, $R^3=C(=CH_2)CH_3$
17 1αH, $R^1=OH$, $R^2=CH_3$, $R^3=C(=CH_2)CH_3$

Fig. 1 J values in Hz



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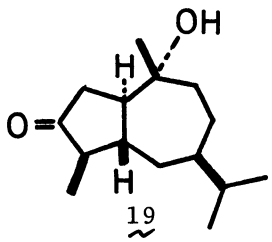

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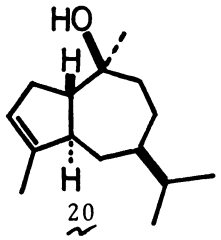

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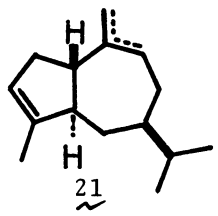

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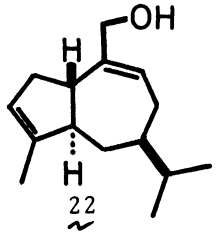

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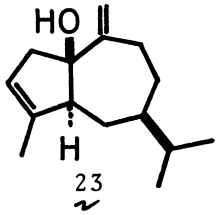

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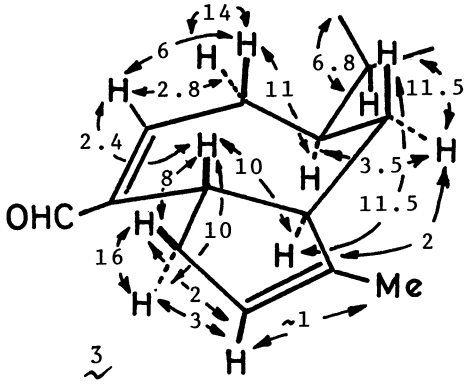
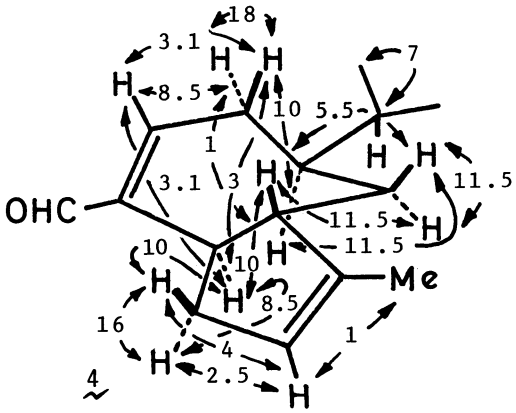


δ 3.12($H_2\alpha$), 2.81(H_1), 2.45($H_2\beta$), 2.43($H_8\alpha$)
2.22($H_8\beta$), 2.19($H_6\alpha$), 2.11(H_5), 1.65(H_{11})
1.32(H_7), 1.26($H_6\beta$)



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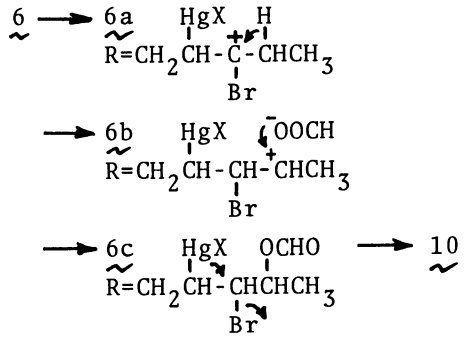
δ 2.95($H_2\alpha$), 2.81(H_1), 2.63(H_5), 2.40($H_8\beta$)
2.31($H_6\alpha$), 2.12($H_2\beta$), 1.82($H_6\beta$), 1.75(H_7)
1.63(H_{11}), 1.38($H_6\alpha$)

Scheme 1



11: m/z 266.1868 (ν(neat) 1731, 1713 cm^{-1}), δ($CDCl_3$, 400 MHz), 8.02(1H, s), 5.59(1H, dt, J=14.5, 7), 5.51(1H, dd, J=14.5, 6.1), 5.41(1H, quint, J=6.1), 1.33(3H, d, J=6.1), 0.99 and 0.97(1:1)(3H, each s), 0.91 and 0.90(each 3H, d, J=6.1). Isomeric mixture.

7) R. B. Bates, G. Buchi, T. Matsuura, and G. H. Posner, J. Am. Chem. Soc., 82, 2327 (1960).

8) R. Howe and F. J. McQullin, J. Chem. Soc., 1956, 2670.

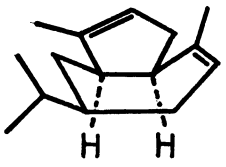
9) A mixture of 12 and 13 (10:3) was obtained from 5 and N,N-diethyl-1-amino-3-pentanone (50%). However, separation of the mixture was difficult. Hitherto, pure 12 and 13 were obtained from natural products.[7,8]

10) For a similar sequence of reactions see E. Piers and K. F. Cheng, Can. J. Chem., 45, 1591 (1967).

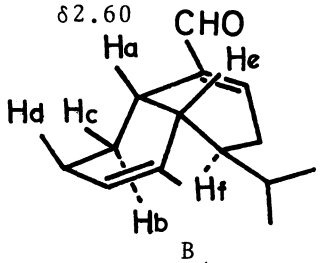
11) E. Piers and K. F. Cheng, ibid., 48, 2234 (1970).

12) E. Piers and R. J. Keziere, ibid., 47, 137 (1969) and refs. therein.

13) Cis-guaianoids corresponding to 2 and 4 are not suitable as structure of sclerosporal, since models shown that these cis compounds will not exhibit a coupling constant 12.4 Hz at δ 2.60(1H, bd, not coupled with δ 6.81, assigned in ref 2 to C-1 proton), irrespective of their possible stable conformations, such as A. In such cis fused cyclopentene compounds J_{vic} smaller than 10 Hz and J_{gem} larger than 14 Hz, but not J 12.4 Hz are expected for protons on the five membered ring. It appears that the reported[1] nmr data at 100 MHz are explained rather by assuming formula B for sclerosporal. Line broadening at δ 2.60 may then be accounted for by weak couplings between H_a-H_c and H_a-H_e as well as virtual couplings between H_a-H_d and H_a-H_f. Recently, Katayama, Marumo and Hattori have proposed formula B mainly on the basis of the nmr spectral analysis at 360 MHz(Annual Meeting of the Agricultural Society of Japan, April 1982, Abstr. p. 556).



A



B

14) Most part of this paper was presented before the 45th National Meeting of the Chemical Society of Japan on April 1982, Abstr. II, 759.

(Received August 3, 1982)